REMARKS

Prior to the present amendment, claims 15-18, 21-23, 25-27 and 38-42 were pending. By this amendment, applicants have cancelled claims 17, 18 and 25-27. Accordingly, claims 15, 16, 21-23 and 38-42 are currently pending.

The Invention

The inventors have discovered that mucosal administration of a mixture of a Hepatitis B virus surface antigen (HBsAg) and a second vaccine antigen which is a viral nucleocapsid or a virus-like particle is effective in generating an immune response. The immune response generated is useful for the prevention or treatment of an infection by either hepatitis B virus, or the agent from which the second vaccine antigen is derived. Further, the inventors surprisingly discovered that HBsAg has an adjuvant effect on the second vaccine antigen.

Office Action

On page 2 of the office action, claims 15, 16 and 21-23 were rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Tabor et al. (U.S. Patent No. 4,547,368) in light of Bowen et al. (*Research Virology*, 1992, 143:269-278, abstract only). The examiner states that Tabor et al. teaches a combination vaccine formulation comprising a mixture of 20 μg of HBsAg and 50 μg of Hepatitis B nucleocapsid.

Applicants respectfully disagree. The claimed invention is restricted to vaccine formulations suitable for mucosal administration containing HBsAg antigen and a second vaccine antigen which is a viral nucleocapsid or a virus-like particle. There is no disclosure or suggestion in Tabor et al. of a formulation for mucosal administration having HBsAg antigen and a viral nucleocapsid or a virus-like particle.

Further, the claimed invention requires that the HBsAg has an adjuvant effect on the viral nucleocapsid or virus-like particle. There is no disclosure or suggestion in Tabor et al. that the HBsAg antigen has an adjuvant effect on HBcAg.

Accordingly, the claimed invention is not anticipated by the cited reference. Therefore, applicants respectfully request that the rejection of the claims under 35 U.S.C. 102(b) be reconsidered and withdrawn.

On page 3 of the office action, claims 17, 25, 27 and 38-41 were rejected under 35 U.S.C. 103(a) for allegedly being obvious over Tabor et al. in light of Bowen et al., and further in view of Rose et al. and Hauser et al.

Merely in order to expedite prosecution, claims 17, 25 and 27 have been canceled. Therefore, the rejection is moot and should be withdrawn.

With respect to claims 38-41, the primary reference cited is Tabor et al. As stated above in the response to the 102(b) rejection, the claimed invention is restricted to vaccine formulations suitable for mucosal administration. There is no disclosure or suggestion in the cited references of a formulation containing HBsAg antigen and a viral nucleocapsid or a virus-like particle for mucosal administration. Further, there is no disclosure or suggestion in the cited references that the HBsAg has an adjuvant effect of the second or third vaccine antigen.

Accordingly, the claimed invention is not obvious over the cited references. Therefore, applicants respectfully request that the rejection of the claims under 35 U.S.C. 103(a) be reconsidered and withdrawn.

On page 3 of the office action, claims 15, 18 and 26 were rejected under U.S.C. 103(a) for allegedly being obvious over Wands et al. Claims 18 and 26 have been

cancelled. Therefore, the rejection of claims 18 and 26 is moot and should be withdrawn. The comments below apply to the rejection of claim 15.

The examiner states that Wands et al. discloses a fusion protein containing HBsAg and HCV core proteins. The examiner contends that presentation of the unfused HBsAg and HCV core antigens is equivalent to the presentation of HBsAg and HCV antigens in the fusion protein of Wands et al.

Applicants respectfully disagree. The presentation of unfused HBsAg and HCV core antigens is **not** necessarily equivalent to the presentation of the antigens in a fusion protein for the reasons given below.

First, the antigens in a fusion protein are attached to each other. Therefore, the antigens in the fusion protein of Wands et al. are made in the same cell and necessarily come in contact with the same cell. However, if the antigens are unfused, the unfused antigens may not contact the same cell.

Second, the antigenic epitope of each separate antigen may have a different conformation in a fusion protein due, for instance, to steric hindrance. However, if the antigens are unfused, each antigen retains its native conformation.

Therefore, presentation of unfused HBsAg and HCV core antigens is **not** necessarily equivalent to the presentation of the antigens in a fusion protein, as the examiner asserts.

Further, in order to constitute a reference against claim 15, there must be motivation apparent in Wands et al. to convert fused antigens to unfused antigens. The examiner has not, however, provided the requisite motivation. Absent such motivation, a *prima facie* case of obviousness does not exist.

Accordingly, applicants respectfully request that the rejection of the claims under 35 U.S.C. 103(a) over Wands et al. be reconsidered and withdrawn.

On page 4 of the office action, claims 17, 18, 25, 26 and 27 were rejected under 35 U.S.C. 112, first paragraph allegedly for lacking enablement. Merely in order to expedite prosecution, applicants have cancelled these claims. Accordingly, the rejection is now moot and should be withdrawn.

On page 7 of the office action, claim 42 was rejected under 35 U.S.C. 103(a) for allegedly being obvious over Tabor et al. in view of McCluskie et al. (*Viral Immunol*, 1998, 11:245-252). The examiner states that Tabor et al. discloses a vaccine formulation comprising a mixture of HBsAg and hepatitis B nucleocapsid for subcutaneous administration. The examiner acknowledges that Tabor et al. does not disclose mucosal administration of the vaccine formulation.

To rectify the deficiency, the examiner cites McCluskie et al. According to the examiner, McCluskie et al. discloses the mucosal administration to mice of a vaccine formulation containing HBsAg complexed with antibodies against HBsAg for generating an immune response. Therefore, the examiner contends that it would be obvious to combine the vaccine composition of Tabor et al. and the mucosal administration of McCluskie et al.

Applicants respectfully disagree. The examiner, on page 7 of the office action, refers to McCluskie et al. as stating the following: "Administration of a vaccine to a mucosal surface can induce both systemic and mucosal immune responses, whereas parenteral administration will usually induce only systemic immunity."

The above quote in McCluskie et al. neither discloses nor suggests that a vaccine that can be administered parenterally can necessarily also be effectively administered mucosally. Rather, the above quote is a general statement regarding the type(s) of

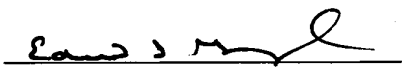
immune response generated by mucosal and parental administration. Moreover, McCluskie et al. does not state that mucosal administration will necessarily induce an immune response. Rather, McCluskie et al. states that mucosal administration "can induce" an immune response.

There is no disclosure or suggestion in either Tabor et al. or McCluskie et al. that a vaccine formulation containing HBsAg and hepatitis B nucleocapsid delivered by the mucosal route will induce an immune response. Thus, the claimed invention is not obvious over Tabor et al. in view of McCluskie et al.

Accordingly, applicants respectfully request that the rejection of the claims under 35 U.S.C. 103(a) over Tabor et al. in view of McCluskie et al. be reconsidered and withdrawn.

For the above reasons, allowance of the pending claims is earnestly requested. If the examiner has any questions or concerns regarding this matter, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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